#24
P78/10/01

Docket Number: 47,653.2 (1789)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	J.C. Houck, et al.		
Serial Number:	09/190,043	Art Unit:	1631
Filed:	November 10, 1998	Examiner:	M. Borin
For:	SMALL PEPTIDES AND METHODS FOR TREATMENT OF ASTHMA AND INFLAMMATION		

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on July 16, 2001.

Rita Johnson
Rita Johnson

BRIEF ON APPEAL

This is an appeal from the final rejection dated August 14, 2000 (Paper Number 14) wherein claims 1-3 are under examination and rejected. Three copies of this Brief are enclosed.

BRIEF ON APPEAL FEE

A check for $155.00, the required fee for filing a Brief on Appeal, is enclosed herewith.

REAL PARTY IN INTEREST

The real party in interest is Histatek, LLC, a Delaware corporation. The assignment of the inventors to this corporation was recorded at Reel/ Frame 9761/0597 and 9740/0356.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to Appellant, Appellant's legal representative or the assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

STATUS OF THE CLAIMS

Claims 1-3 stand final rejected. Claims 4-20 are withdrawn from consideration due to a restriction requirement. Claims 1-3 are on appeal.

STATUS OF THE AMENDMENTS

Claim 1 was amended in a communication filed June 12, 2000. No other amendments have been made.

SUMMARY OF THE INVENTION

The invention is directed to a method of treating an allergy reaction in a mammal by administering to the mammal an anti-allergic effective amount of the formyl peptide, f-Met-Leu-Phe-Phe (page 7, lines 12-19), to which reference is made

also as "HK-X" (page 22, line 19). The peptide is prepared by conventional small peptide chemistry techniques (page 12, lines 20-23). Methods of using pharmaceutical compositions, including doses, routes of administration, pharmaceutical carriers, etc. are described at page 12, line 25 through page 18, line 7. The claimed peptide is useful for treating allergies such as allergic rhinitis, uticaria, anaphylaxia, drug sensitivity and food sensitivity (page 7, lines 1-3). The claimed peptide can be administered in combination with a second active ingredient, for example, antileukotrienes, $beta_2$ agonists, corticosteroids, and the like (page 9, lines 20-24).

The examples describe a well established mouse model for assessing the treatment effect of compounds on inhaled allergens. Allergic response is induced by treating the mice with OVA, which manifests in mucous accumulation in the airways. It was found that the claimed peptide inhibits mucous accumulation at least as effectively as a well known pharmaceutical, Zileuton® (page 21, line 10 - page 40, line 25).

ISSUE(S)

1. Claims 1 and 2 are rejected under 35 U.S.C. § 103(a) over Gleisner (*Inflammation* **5**, 13-17, 1981) in view of Oxford Dictionary of Biochemistry and Molecular Biology (1981) and Casale (*Annals of Allergy*, Vol. 1 (1983)) and Dimitrascu (Abstract of *Rev. Roum. Med. Interne* (1996), 34(3-4), 159-172), and further in view of Kermode (*Biochem. J.*, 276, 715-723 (1991)).

2. Claim 3 is rejected under 35 U.S.C. § 103(a) for the same reasons as set forth in the rejection of claims 1 and 2, and further in view of Goodman and Gilman (p. 170, reference AL (*The Pharmacological Basis of Therapeutics*, 6th Ed. 170-171 and 1490 (1980))

GROUPING OF THE CLAIMS

All claims stand or fall together for the purpose of the present appeal.

ARGUMENT

Summary Of The Argument

The cited art, as a whole, teach that f-methionyl peptides are inflammatory agents. Although Gleisner (1981) suggests that some f-methionyl peptides inhibit degranulation of mast cells and could potentially be a useful addition to the antihistaminic drugs, later publications by Ferry (1989), Kermode (1991) and Anderson (1992), of record, teach that f-methionyl peptides are inflammatory agents. Gleisner says nothing specific about f-Met-Leu-Phe-Phe. However, Kermode states that f-Met-Leu-Phe-Phe was the most potent of the seven formyl peptide analogs tested for stimulation of degranulation and chemotaxis including the f-Met-Leu-Phe compound of Gleisner.

F-methionyl peptides have been used to study ant understand the inflammatory response, such as caused by infection with bacteria. There has never been even a hint of a suggestion that a doctor should treat an infection with fMLP.

Indeed, such a treatment would aggrevate the pro-inflammatory response already caused by the infection and create further damage to tissue. (Declaration of Dr. Lipani, paragraph 10) No doctor would administer a pharmacological composition to induce a "pro-inflammatory" response. (Declaration of Dr. Lipani, paragraph 12)

None of the cited art, nor any publications of which Applicant is aware, teach the use of the presently claimed f-Met-Leu-Phe-Phe as a pharmaceutical composition for any beneficial purpose. Much less is there any suggestion that f-Met-Leu-Phe-Phe has an anti-inflammatory effect or is useful for treating an allergic reaction.

Only the present Applicant has discovered and taught this use.

Thus, it is not seen how the present invention would have been obvious to one of ordinary skill in the art.

It is respectfully submitted that the examiner has not made out even a *prima facie* case of obviousness. The cited art, as a whole, teach away from the present invention. However, even if there were some suggestion for the present invention in the cited art, the surprising and unexpected results provided by the peptide f-Met-Leu-Phe-Phe could not have been reasonably predicted even by those skilled in the art, much less by one of ordinary skill in the art.

The examiner states that Kermode teaches that f-Met-Leu-Phe and f-Met-Leu-

Phe-Phe are functional equivalents. In fact, Kermode, Ferry and Anderson, as a whole, show that different formyl Met peptides are **not** functional equivalents. Further, the tests conducted by Dr. Clagett and submitted with his declaration (of record) show that the first compound has no anti-inflammatory effect while the second (claimed) compound has substantial anti-inflammatory effect. Thus, the claimed compound, f-Met-Leu-Phe-Phe, is clearly not the functional equivalent of f-Met-Leu-Phe.

The Cited Art

Gleisner et al.

In 1981, Gleisner et al. reported, based on semiquantitative results, that pepstatin and N-formyl peptides can prevent mast-cell degranulation produced by 48/80, lung permeability factor, and anti-rat IgE, when tested using the rat skin model. They stated that f-Met-Leu-Phe was the most potent inhibitor of mast cell degranulation and, also, that Met-Phe was ineffective (see page 14, Results). The publication concludes that "[t]his finding of small peptides (pepstatin and f-methionyl peptides) capable of inhibiting the degranulation of mast cells is of considerable potential clinical importance.

they do not mention anti-his uses of f-

Oxford Dictionary of Biochemistry and Molecular Biology

This dictionary stated that mast cells are important in the development of allergenic response.

Dumitrascu

Dumitrascu stated that there are two types of mast cells with differences in structure, distribution and function: conjunctival and mucosal. Dumitrascu also stated that mast cells are among the most important cells in the development of allergic inflammation through cytokines and mediators released on the activation of surface receptors.

Casale

Casale stated that mast cells are extremely important mediators in the pathogenesis of asthma.

Kermode et al.

In 1991, Kermode et al. reported that various f-Met peptides are potent **stimualtors** of degranulation. Indeed, Kermode et al. reported that **both f-Met-Leu-Phe and f-Met-Leu-Phe-Phe are potent stimulators** of degranulation of neutrophils and are chemotactic.

Kermode et al. reported a study to determine the mechanism by which formyl peptides stimulate neutrophil degranulation and chemotaxis (page 715, column 2, lines 3-15):

> One proposal for the neutrophil is that the **high-affinity form of the receptor** may be responsible for activation of some biological functions, notably chemotaxis, with the **low-affinity form** responsible for other functions, e.g. degranulation. Similar proposals have been made to explain the differential activation of a range of biological responses in

> several other cell types and with several other receptor agonists. The only evidence to date to support this hypothesis for the neutrophil, however, is derived from studies of the influence of various perturbations of the cell on both the receptor-binding pattern and the biological responses for a single chemotactic formyl peptide, the prototypical compound N-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMet-Leu-Phe). [Emphasis added].

Kermode tests several different formyl peptides, including f-Met-Leu-Phe, and categorizes them into "most potent" and "less potent". Furthermore, Kermode concludes that the "most potent" peptides bind to the high affinity form of the receptor, and that the "less potent" peptides bind to the low affinity form of the receptor. The "most potent" peptides according to Kermode are f-Met-Leu-Phe-Phe and f-Met-Leu-Phe-NHBzl. The "less potent" peptides are f-Met-Leu-Phe, f-Nle-Leu-Phe, f-Nva-Leu-Phe and f-Val-Leu-Phe. Thus, even amongst formyl peptides, according to Kermode, there are differences in potencies and in their mechanism of action.

Indeed, for example, Kermode teaches, contrary to Gleisner, that (page 716, right column):

> [t]he logical interpretation of these data is thus that the high-affinity sites are the receptors that **initiate degranulation**. (Emphasis added.)

Because Kermode also teaches that f-Met-Leu-Phe-Phe binds to the high affinity receptor, one skilled in the art would be expected to conclude that f-Met-Leu-Phe-Phe **initiates degranulation** of the neutrophils and thus is harmful.

Kermode postulated that the high affinity site was responsible for activiating chemotaxis, which also is harmful. Thus, it is not seen how any teaching of Kermode would lead one of ordinary skill in the art to make a pharmaceutical composition.

Goodman and Gilman

Goodman and Gilman (reference AL) provide a general discussion on drug absorption, bioavailability and routes of administration showing the state of the art in 1980. There is no mention whatsoever of f-methionyl peptides.

Anderson et al.

Anderson et al. (reference AC) is not presently being relied on by the examiner. However, it is considered that the teachings of Anderson et al. are important for illustrating the state of the art at the time of the present invention.

In 1992, Anderson et al. reported structure activity studies of f-methionyl peptides. First, the types of disorders that may be associated with formyl peptides are listed and then a mechanism for the cause of such disorders is suggested (page 249, first column, lines 1-10; page 254, second column, lines 32-41):

> **There is now a substantial body of evidence implicating bacterial F-met peptides in intestinal inflammatory disorders**. They induce adhesion, chemotaxis, superoxide production, and lysosomal enzyme release in neutrophil leukocytes; **can induce experimental colitis** in mice, rats, and rabbits; **increase intestinal vascular and mucosal permeability**; stimulate intestinal leukotriene synthesis; and are **spasmogenic for gut smooth muscle**.

* * *

> Using a radioimmune assay with a rabbit polyclonal antibody raised against FMLP, we have identified FMLP immunoreactivity in both rat and human bile. The most likely source of this reactivity is formyl oligopeptide produced by intestinal bacteria and reaching the liver in portal blood. **Since the liver excretes such peptides in a largely unaltered form, they presumably retain their potential to induce inflammatory responses should they cross the biliary epithelium**. [Emphasis added].

Anderson concludes that (page 255, column 1):

> The association between biliary tract disorders and inflammatory bowel disease has long been thought to be related to the presence of bacterial products in bile, **and low-molecular-weight formyl-peptides could be important in this respect**. [Emphasis added].

Thus, the Anderson reference also **teaches away** from using formyl peptides and their analogues as for therapy. The studies of Anderson also support the notion that formyl peptides and their analogues may **cause inflammatory disorders** and thus **would not be useful** as pharmaceutical compounds.

Ferry et al.

Ferry et al. (reference AM) also is not presently being relied on by the examiner. However, it is considered that the teachings of Ferry et al. also are important for illustrating the state of the art at the time of the present invention.

In 1989, Ferry et al. recognized f-Met peptides as pro-inflammatory peptides. In fact, Ferry taught that administration of low molecular weight formyl peptides is **pro**inflammatory and, by whatever route, could cause **unwanted reactions or disorders**. For example, Ferry states on page 64, second column under Discussion:

> There is an increasing body of evidence suggesting that low molecular weight **proinflammatory** N-f-met oligopeptides **could play a**

> **role in intestinal inflammatory disorders**. All species of intestinal bacteria so far investigated produced such peptides in vitro and bioactive peptides have been demonstrated in colonic fluid obtained by in vivo dialysis techniques.
>
> In experimental animals **both colonic infusions and rectal administration of N-formyl methionyl-leucyl-phenylalanine (N-f-met-leu-phe) resulted in experimental colitis**, although the concentrations used in these studies were in the millimole range, at least three orders of magnitude greater than those estimated by bioassay of intestinal contents.
>
> **Systemic infusion** of radiolabeled f-met peptides in rats showed that intact peptide was rapidly excreted in bile and an enterohepatic circulation of f-met peptide was subsequently demonstrated. **Experimental acetic acid-induced colitis was associated with an eightfold increase in biliary excreation of labeled peptide following its instillation into colon loops**. [Emphasis added].

Thus, Ferry concluded from their own experimental data that (page 61, first column, lines 19-28):

> in the ileum both enzymic degradation and restricted mucosal permeability contribute to the intestinal barrier to luminal bacterial formyl oligopeptides. In the colon, however, enzymic mechanisms are less active and restricted mucosal permeability is the major factor. **Abnormalities of the intestinal mucosal barrier to proinflammatory bacterial peptides could play a role in inflammatory disorders of the gut**. [Empahsis added.]

Although their conclusion focuses on administration of formyl peptides to the **unhealthy** intestine, they also suggest problems even if administered to **healthy** individuals. Ferry admits that their failure to find increased absorption to the intestine under normal conditions cannot in any way be used even to assume, much less to predict with reasonable certainty, that these peptides will have no adverse effect when administered to healthy individuals (paragraph bridging pages 65-66):

> **Changes in vascular permeability and blood flow (without changes in mucosal permeability) have been reported with f-met-leu-**

> **phe in rat small intestine** by Granger et al. and these effects were apparently not found in animals rendered neutropenic, suggesting an effect of f-met-leu-phe on neutrophil leukocytes in the microcirculation of the gut. More recently, **the same group reported increased mucosal permeability in response to ileal perfusion with f-met-leu-phe** (10^{-6}M). This observation supports that of Magnussen et al. The effect appears to be confined to the terminal ileum and to be leukocyte-dependent. **We failed to find increased ^{51}Cr-EDTA absorption with either f-met-leu-tyr (10^{-4}M) or f-met-leu-phe (10^{-4}M) alone over a 1-h period. The short period of observation and the infusion into loops rather than perfusion design may account for this. Our studies were simply designed as controls for our experiments with different agents rather than to investigate the inflammatory response and permeability changes secondary to leukocyte accumulation. Trace amounts of intact formyl peptides do escape the enzyme and mucosal permeability barriers and trace amounts of intact peptide (picomoles) were recovered in bile in our control studies**. The biological significance of these amounts awaits further studies. [Emphasis added].

Ferry suggests that the trace amounts of formyl peptide in bile **may be** a symptom of potential adverse effects even under healthy conditions but has not investigated this issue. However, based on the wealth of information provided by others, it is submitted that one of ordinary skill in the art would consider it quite likely that trace amounts of formyl peptide in bile is a symptom of potential adverse health effects.

Ferry and Anderson support Kermode in teaching that f-Met peptides cause harmful effects. In view of these teachings, why would one of ordinary skill in the art even consider the use of f-Met peptides for treatment of an allergy reaction.

Indeed, although there are extensive publications relating to f-Met peptides, to

Applicant's knowledge, none of them suggest administering such peptides for any beneficial effect.

Applicants arguments are supported by two declarations of Dr. Clagett and the declaration of Dr. Lipani.

Detailed Discussion Of The Rejections

1. Claims 1 and 2 are rejected under 35 U.S.C. § 103(a) over Gleisner (*Inflammation* **5**, 13-17, 1981) in view of Oxford Dictionary of Biochemistry and Molecular Biology (1981) and Casale and Dimitrascu, and further in view of Kermode.

2. Claim 3 is rejected under 35 U.S.C. § 103(a) for the same reasons as set forth in the rejection of claims 1 and 2, and further in view of Goodman and Gilman (p. 170, reference AL (*The Pharmacological Basis of Therapeutics*, 6th Ed. 170-171 and 1490 (1980))

There is no suggestion in Gleisner that all f-Met peptides are effective inhibitors of degranulation. Nor is there any specific teaching that the presently claimed f-Met-Leu-Phe-Phe inhibits degranulation. Table 1 at page 20 of the present specification clearly shows that all f-Met-Leu peptides are not inhibitors of degranulation. Further, the presently claimed f-Met-Leu-Phe-Phe exhibits surprising and unexpected degranulation inhibition properties, when compared to the f-Met-Leu-Phe of Gleisner et al.

Gleisner suggests that f-Met-Leu-Phe may have an inhibiting effect on mast cell degranulation but fails to show any inhibiting effect for other formyl peptides. For example, Table 1 on page 15, shows that the closely related peptides f-Met-Phe and

Met-Phe had little inhibitory effect on mast cell degranulation. It is **not** obvious from Gleisner that structurally similar compounds will have the same effect or the same potency.

Furthermore, Gleisner did **not** test the presently claimed f-Met-Leu-Phe-Phe. Later references, such as Kermode, Ferry and Anderson, which do address the claimed peptides, teach that these peptides have pro-inflammatory activity and thus would stimulate the response to an allergic reaction, not treat it.

Most importantly, Gleisner ***fails*** to teach or suggest anything regarding the presently claimed method for treating an allergy reaction in a mammal comprising administering to the mammal an anti-allergic effective amount of **f-Met-Leu-Phe-Phe**.

Applicants have tested the effects on inflammation (i.e. allergic response) induced by prior art peptides, namely fMLP (f-Met-Leu-Phe) discussed in Gleisner and other references, as compared to peptides of the present invention, namely fMLPP (f-Met-Leu-Phe-Phe). The results of these experiments are presented in the Declaration (06/9/00) of Dr. Clagett (of record). Briefly, Applicants compared the effects of injecting fMLP or fMLP + fMLPP into the dorsum of mice feet and observed the effects on the injected tissue over time. Applicants found that injection of fMLP alone caused a strong inflammatory effect including massive cellular infiltration to the site of injection whereas simultaneous injection with fMLPP blocked this inflammatory response. See the Declaration (06/9/00) of Dr. Clagett, paragraphs 10-12.

In short, fMLP exhibited a **pro**-inflammatory or allergy stimulating activity in accord with the teachings of the prior art. However, surprisingly and unexpectedly (in view of the prior art) fMLPP of the present invention exhibited an **anti**-inflammatory activity that blocked the pro-inflammatory response induced by fMLP. See the Declaration (06/9/00) of Dr. Clagett, paragraphs 13-16.

The Examiner alleged the declaration was not sufficient because it failed to demonstrate the effect of f-Met-Leu-Phe-Phe when used alone. The examiner stated:

> [T]he Clagett declaration [which] presumably demonstrates unexpected anti-inflammatory effect of f-Met-Leu-Phe-Phe. Note, however, the essential difference in the effect of a biological mediator (such as chemotactic f-Met peptide) when it is used alone as compared to its use in the presence of another pro-inflammatory agent. Cellular response to f-Met peptides (which can be described as inflammatory response) is the same type of protective reaction which mediates response to foreign infection. It is well known in the art that biological mediators such as chemotactic factors stimulate the migration of neutrophils from the circulation into sites of infection or tissue damage.. . .
>
> Characteristically, in the Declaration filed 06/12/00 [*sic*] the effect of the f-Met-Leu-Phe-Phe (fMLPP) is demonstrated only as an inhibitor of inflammatory effect caused by another f-Met peptide fMLP. The absence in the Declaration of a showing of the effect of fMLPP alone is not surprising because Kermode shows (Table 2) that fMLPP (the peptide of the claimed composition) is more potent chemotactic agent and stimulator of neutrophil degranulation than fMLP (the peptide used as "pro-inflammatory" agent). One would expect that fMLPP, alone, would be at least as "pro-inflammatory" as fMLP. There is no proper comparison in effects of the two formyl peptides used in the Declaration to demonstrate unexpected results.

Applicants have found that such *in vitro* tests are not a predictor of the bioactivity of fMLPP *in vivo*. Although based on the teachings of the prior art, " [o]ne

would expect that fMLPP, alone, would be at least as 'pro-inflammatory' as fMLP," as concluded by the examiner, that is an erroneous expectation. Further, based on the teachings of the prior art, one of ordinary skill in the art would not expect fMLPP to act any differently after prior treatment with fMLP. (Declaration of Dr. Lipani, paragraph 14)

The examiner totally missed the point. There is no teaching in any of the cited art that the claimed f-Met-Leu-Phe-Phe has any anti-inflammatory effect. F-methionyl peptides, particulary f-Met-Leu-Phe, have been studied because it is considered that the peptide is secreted by bacteria that cause infections and that the peptide produces the inflammation response. Thus, one would expect that the treatment with f-Met-Leu-Phe would produce the inflammatory response. In the test conducted by Dr. Clagett, f-Met-Leu-Phe was used to stimulate the inflammatory reponse. However, one also would expect f-Met-Leu-Phe-Phe to stimulate the inflammatory response (as taught by Kermode and admitted by the examiner). Yet, the administration of f-Met-Leu-Phe-Phe by Dr. Clagett had the opposite effect from what would have been expected. Instead of further stimulating the inflammation response, the f-Met-Leu-Phe-Phe provided an anti-inflammatory response that inhibited the effect of f-Met-Leu-Phe. That is, indeed, a surprising and unexpected result of f-Met-Leu-Phe-Phe, and contrary to the teachings of the prior art.

Nevertheless, even though Applicant disagreed with the examiner, to expedite prosecution, a second Declaration (1/15/01) by Dr. Clagett was submitted. The

second declaration presents tests illustrating the effects of fMLP alone, and of HK-X (fMLPP) both alone and in conjunction with fMLP in the mouse model. The results of these experiments are surprising and unexpected in view of the prior art teachings for f-Met peptides.

Briefly, in the experiments, there was subcutaneously injected into the dorsum of mice feet 200 μg of **fMLP** alone; 200 μg of HK-X (fMLPP) alone; 200 μg of fMLP and 200 μg of HK-X together; and as a control the vehicle (4% DMSO in Tyrode's solution).

The results showed that fMLP alone induced a potent chemotactic response. However, by itself, HK-X (fMLPP) was **not** chemotactic and HK-X **inhibited** the chemotactic capacity of fMLP when HK-X (fMLPP) and fMLP were administered together. Therefore, HK-X (fMLPP) mechanism of action functions at the **earliest** stage of inflammation by **inhibiting** the recruitment of inflammatory cells. A second important property of HK-X (fMLPP) is that it also **inhibits** the action of a potent chemotactic agent.

The Oxford dictionary of Biochemistry and Molecular Biology (1981) fails to make up for the deficiencies of Gleisner. Although it teaches that mast cells are important in the development of allergenic response, there is no teaching or suggestion that f-Met-Leu-Phe-Phe is an anti-inflammatory or can be used to treat an allergic response.

The Oxford dictionary of Biochemistry and Molecular Biology (1981) teaches that antihistamines are used to treat allergic reactions. However, there is no teaching or suggestion that f-Met-Leu-Phe-Phe can act as an antihistamine.

Dumitrascu and Casale teach that mast cells are important in the development of allergenic response. However, there is no teaching or suggestion that formyl Met peptides would be useful for treating an allergic reaction.

Dumitrascu and Casale also fail to make up for the deficiencies of Gleisner.

The present application surprisingly and unexpectedly teaches that f-Met-Leu-Phe-Phe has an inhibitory effect on **both** mast cells and neutrophils. Applicant has discovered that f-Met-Leu-Phe-Phe **inhibits** inflammation at the **earliest stages** by inhibiting the recruitment of inflammatory cells to the site of inflammation.

The fact that Casale and Dumitrascu teach that mast cells are important in the mechanism of asthma does not make the present invention obvious.

Kermode et al. teach that various f-Met peptides are potent stimualtors of degranulation. Indeed, Kermode et al. teach that both f-Met-Leu-Phe and f-Met-Leu-Phe-Phe are potent stimulators of degranulation of neutrophils are chemotactic. Thus, Kermode et al. not only fail to make up for the deficiencies of Gleisner, but also

provide teachings contrary to Gleisner. Such characteristics and pro-inflammatory activity would lead one skilled in the art away from the use of the presently claimed f-Met-Leu-Phe-Phe to treat allergy.

Kermode makes **no** suggestion for using formyl peptides for any therapy . There is not even a hint of a suggestion by Kermode that such peptides will be useful for any therapeutic treatment.

Indeed, for example, Kermode teaches, contrary to Gleisner, that (page 716, right column):

> [t]he logical interpretation of these data is thus that the high-affinity sites are the receptors that **initiate degranulation**. (Emphasis added.)

Because Kermode also teaches that f-Met-Leu-Phe-Phe binds to the high affinity receptor, one skilled in the art would be expected to conclude that f-Met-Leu-Phe-Phe **initiates degranulation** of the neutrophils and thus is harmful.

Earlier Kermode postulated that the high affinity site was responsible for activiating chemotaxis, which also is harmful. Thus, it is not seen how any teaching of Kermode would lead one of ordinary skill in the art to make a pharmaceutical composition as claimed herein. Indeed, the first discovery that the claimed f-Met peptides provide useful biological properties was made by Applicant. Indeed, this useful property has been found only in the few claimed peptides, not in all f-Met peptides.

The examiner cites Kermode [sic, reference AE], *Biochem. J.* (1991) **276**, as disclosing that formyl Met peptides, such as f-Met-Leu-Phe and f-Met-Leu-Phe-Phe are functional equivalents. However, contrary to the suggestion of Gleisner et al., Kermode et al. teach that formyl peptides, particularly, f-Met-Leu-Phe-Phe, stimulate the degranulation of neutrophils and chemotaxis. That is an inflammatory response and is **not** desirable for treating allergies.

It is clear from the tests conducted by Dr. Clagett and submitted in the two declarations that f-Met-Leu-Phe and f-Met-Leu-Phe-Phe are **not** functional equivalents. Further, it is not seen how the properties discovered by Applicants for f-Met-Leu-Phe-Phe would have been reasonably predictable from the published properties of f-Met-Leu-Phe, or the prior art as a whole.

Applicants teach that f-Met-Leu-Phe-Phe **inhibits** all of the above responses. Based on the properties of f-Met-Leu-Phe-Phe as described by Gleisner et al. and Kermode et al, it would not have been obvious to anyone skilled in the art, much less one of ordinary skill in the art, to use f-Met-Leu-Phe-Phe for the treatment of an allergic reaction, i.e., for **downregulation** of the inflammatory response.

Prior to the present discovery by Applicants, no one would have considered the use of f-Met-Leu-Phe-Phe to treat an allergic reaction. See the Declaration of Dr. Lipani, paragraph 19.

Only present Applicant has discovered the usefulness of administering the peptides of the claimed invention as a method for treating an allergy reaction.

None of the cited references, taken alone or in any combination, teach that f-Met-Leu-Phe-Phe has anti-inflammatory effect or is useful for treating allergic reactions.

The surprisingly remarkable inhibitory activities of the peptides of the present invention would not have been obvious to one of ordinary skill in the art from the prior art teachings. See the Declaration of James Clagett, paragraphs 7-16.

Accordingly, applicants respectfully submit that the combination of Gleisner, in view of Oxford dictionary of Biochemistry and Molecular Biology (1981) and Casale and Dumitrascu, and further in view of Kermode, does not teach or suggest the presently claimed invention to one of ordinary skill in the art.

Thus, given the many teachings that f-Met peptides are harmful and corresponding the lack of incentive to administer the f-Met peptides for therapeutic effect, one of ordinary skill in the art would not have been motivated to make and use a pharmaceutical compound for the formyl peptides of the present invention. As noted by Kermode (as cited above), local and systemic administration of f-Met peptides have both been associated **to induce** intestinal inflammatory disorders.

The examiner suggested that one may administer f-Met-Leu-Phe to stimulate response to an infection. There has never been even a hint of a suggestion that a doctor should treat an infection with fMLP. Indeed, such a treatment would aggrevate the pro-inflammatory response already caused by the infection and create further damage to tissue. (Declaration of Dr. Lipani, paragraph 10) No doctor would administer a pharmacological composition to induce a "pro-inflammatory" response. (Declaration of Dr. Lipani, paragraph 12)

In view of the above, it is not seen how the present invention would have been obvious to one of ordinary skill in the art.

A favorable decision reversing the rejections of the examiner is respectfully requested.

Respectfully submitted,

Date: 16 July '01

By _____
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APPENDIX

Claims on Appeal

1. A method for treating an allergy reaction in a mammal comprises administering to the mammal an anti-allergic effective amount of f-Met-Leu-Phe-Phe.

2. The method of claim 1, wherein the allergy is selected from the group consisting of allergic rhinitis, uticaria, drug sensitivity and food sensitivity.

3. The method of claim 1, wherein another active ingredient is administered with said peptide, said active ingredient being is selected from the group consisting of anti-leukotrienes, $beta_2$ agonists and corticosteroids.